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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 205/04, A61K 31/395

A1

(11) International Publication Number: WO 99/37613

(43) International Publication Date: 29 July 1999 (29.07.99)

(21) International Application Number: PCT/GB99/00223

(22) International Filing Date: 22 January 1999 (22.01.99)

(30) Priority Data:

9801499.6	23 January 1998 (23.01.98)	GB
9824458.5	6 November 1998 (06.11.98)	GB

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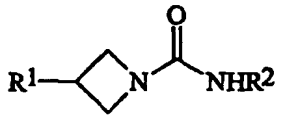
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS



(1)

(57) Abstract

A compound of formula (1), wherein R^1 is aryl; and R^2 is hydrogen or alkyl; pharmaceutically acceptable addition compounds thereof; and their use in therapy, particularly for the treatment and prophylaxis of CNS disorders such as anxiety and epilepsy.

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3NSDOCID: <WO 9937613A1 I >

AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

The present invention relates to chemical compounds useful in the treatment of disorders of the central nervous system (CNS), such as anxiety and all forms of epilepsy, particularly in humans. The invention also relates to the use of such compounds, pharmaceutical preparations containing such compounds and to methods of preparing such compounds.

Anxiety disorders affect an estimated 73 million people world-wide. The benzodiazepines have provided the dominant therapy for anxiety over the past three decades and there is no doubt that they are remarkably effective anxiolytics. However, chronic administration of benzodiazepines produces severe dependence liability, withdrawal syndromes, and side effects (sedation, amnesia, muscle relaxation). The only non-benzodiazepine anxiolytic that has been launched over the past decade is the 5-HT receptor ligand buspirone (Buspar®). This drug has had a remarkable commercial success despite being regarded as a weak anxiolytic (compared with the benzodiazepines) and having a long latency to onset of therapeutic action (2-4 weeks). In addition, buspirone and all related 5-HT_{1A} partial agonists suffer from a dose-limiting side-effect profile comprising nausea, vertigo and endocrine changes.

The aetiology of anxiety disorders is not fully understood, but it is now established that benzodiazepines act by potentiating GABAergic neurotransmission although there is strong evidence that other neurotransmitter systems are modulated indirectly - in particular, the serotonergic and noradrenergic systems. Many pharmaceutical companies have invested considerable resource into the development of serotonergic anxiolytics. However, it is now apparent that ligands selective for 5-HT receptor subtypes, despite displaying anxiolytic-like activity in a restricted range of anxiety models, have, at best, very weak and/or non-dose-related anxiolytic effects in the clinic. The 5-HT_3 receptor antagonists are now discredited as psychotropics: they have a restricted range of activity in functional and anxiety models; they show no convincing anxiolytic effects in the clinic; and they are now accepted only as useful anti-emetics. The 5-HT_{2A} antagonists similarly are regarded as ineffective in terms of psychotropic activity. The clinical utility of 5-HT_{1A} receptor agonists and partial agonists is severely limited by their intrinsically weak action and by the dose-limiting side-effects (vertigo, endocrine changes, nausea) which become more intense as the agonist efficacy of these molecules is increased. The selective CCK_B receptor antagonists have displayed an

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unimpressive preclinical profile similar to that of selective 5-HT ligands such as the 5-HT_3 antagonists.

Serotonergic anxiolytics include the selective serotonin reuptake inhibitors (SSRIs) which, in addition to displaying antidepressant properties, are also effective in anxiety disorders such as panic disorder and obsessive-compulsive disorder. However, as with their antidepressant action, the major drawback with these compounds is the long delay (6-8 weeks) in the onset of clinical improvement following chronic administration.

A strategy in recent years towards improving the clinical profile of classical benzodiazepines is that of developing benzodiazepine receptor partial agonists, according to the rationale that they would have a more selective anxiolytic action and be less liable to induce dependence. However, this approach appears to have failed owing to the very weak anxiolytic actions of these compounds and their poor side-effect profiles (there is either a low or non-existent ratio between anxiolytic and sedative doses).

US-4956359 and EP-A-0194112 disclose 3-aryloxy and 3-arylthio azetidinecarboxamides and their anti-convulsant and anti-epileptic activity. These compounds, like the benzodiazepines, have low water solubility which leads to difficulties in formulation. The presence of an oxygen or sulphur atom, present as a linking atom between the aryl group and the azetidine ring, is a key feature of these compounds since such atoms can undergo hydrogen-bonding interactions with other molecules, affect molecular conformation and increase electron density in the aryl rings.

There remains therefore a need for novel anxiolytic and anti-epileptic agents which do not suffer the above-mentioned drawbacks.

It has now been found that the oxygen and sulphur linking atoms are not necessary for pharmacological action. It is unexpected that compounds in which such atoms are absent exhibit pharmacological activity.

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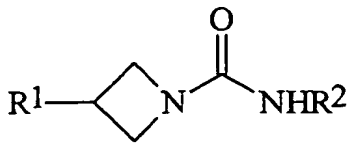
According to the present invention there is provided a chemical compound of formula (1)



(1)

wherein:

R^1 is aryl; and

R^2 is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C_1 to C_{12}, more preferably C_1 to C_8 (such as methyl, ethyl, propyl, isopropyl butyl, isobutyl, tert-butyl, amyl, isoamyl, hexyl, heptyl, octyl).

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl

aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),

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ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonylyoxy, alkycarbonylyoxyalkyl) and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulphur containing groups such as

thiols, thioethers, sulphoxides and sulphones (e.g. alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and

heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl,

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isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, halo, or an halogen-containing group such as trifluoromethyl.

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

The compounds of formula (1) may exist in a number of diastereomeric and/or enantiomeric forms. Reference in the present specification to "a compound of formula (1)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

In the compounds of formula (1), preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl and naphthyl, more preferably R^1 is a substituted phenyl or naphthyl, more preferably R^1 is phenyl or naphthyl having 1 to 3 substituents and most preferably R^1 is phenyl or naphthyl having 1 or 2 substituents. In a preferred embodiment of the invention, R^1 is a mono- or di-substituted phenyl group, preferably a mono-substituted phenyl group.

Where R^1 is napthyl, it is preferred that R^1 is 2-naphthyl.

The preferred substituent groups are selected from halo (preferably fluoro and chloro), trifluoromethyl and tertiary butyl, and more preferably from fluoro, chloro and trifluoromethyl.

Where R^1 is a phenyl having 1 substituent, the phenyl group is preferably para- or meta-substituted. Where R^1 is a phenyl having 2 substituents, the phenyl group is preferably 2,3-disubstituted, 2,4-disubstituted, 3,4-disubstituted or 3,5-disubstituted, preferably 3,4-disubstituted.

Where R^1 is disubstituted, it is preferred that R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group. More preferably, R^1 is dichloro-, difluoro-, chloro-fluoro- or fluoro-trifluoromethyl-substituted.

The R^1 groups are preferably selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

In one embodiment of the present invention R^2 is alkyl, preferably selected from C_{1-8} alkyl, more preferably from alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl and unsubstituted saturated cyclic and acyclic hydrocarbyl, and more preferably from propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

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Particularly preferred compounds are as follows:-

Chirality	R^1	R^2
-	4-Cl-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propynyl
R	4-F-C_6H_4	$MeCH(OH)CH_2$
-	4-Cl-C_6H_4	2-propynyl
R	4-Cl-C_6H_4	$MeCH(OH)CH_2$
S	4-F-C_6H_4	$MeCH(OH)CH_2$
S	4-CF_3-C_6H_4	$MeCH(OH)CH_2$
-	3-CF_3-C_6H_4	2-propynyl
-	4-CF_3-C_6H_4	2-propynyl
R	4-CF_3-C_6H_4	$MeCH(OH)CH_2$
-	4-CF_3-C_6H_4	H

Of these, the preferred compounds are: 3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide, (*S*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide and 3-(4-(Trifluoromethyl)phenyl)-N-azetidine-1-carboxamide.

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According to a further aspect of the present invention there is provided a compound according to the present invention for use in therapy.

The compounds of the present invention may be used in the treatment (including prophylaxis) of CNS disorders. In particular, the compounds of the present invention may be used in the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases (for example, senile dementia) and symptoms related to withdrawal from substance abuse. The compounds may also be used in the relief of spasticity. The compounds of the present invention may also be used in muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

In a preferred embodiment of the present invention, the compounds are used in the treatment (including prophylaxis) of anxiety or epilepsy.

Anxiety includes generalised anxiety disorder (GAD), panic disorder, panic disorder plus agoraphobia, simple (specific) phobias (e.g. arachnophobia, performance anxiety such as public speaking), social phobias, post-traumatic stress disorder, anxiety associated with depression, and obsessive compulsive disorder (OCD).

Epilepsy is a chronic disorder characterised by recurrent seizures. Two forms of epilepsy exist - partial and generalised epilepsy - and each type is subdivided into idiopathic (cause unknown) or symptomatic (cause known). There are two fundamental types of seizures: partial seizures which includes simple partial seizures, complex partial seizures, and partial seizures secondarily generalised; and generalised seizures which includes generalised tonic-clonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, and tonic seizures.

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome,

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chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity, and more preferably anxiety or epilepsy.

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

The invention further provides a method of treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse and spasticity, and more preferably anxiety or epilepsy, comprising administering to a patient in need of such treatment an effective dose of a compound according to the present invention.

The invention further provides a method of muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to the present invention.

According to a further aspect of the present invention there is provided a method of preparing a compound of the present invention.

Compounds of the present invention may be prepared according to the reaction scheme (where P is a nitrogen protecting group). R^1 and R^2 are as previously defined. The 3-aryl-3-azetidinol (III) may be formed by treatment of the ketone (II) with an organometallic reagent such as an aryllithium or an arylmagnesium halide. Removal of the hydroxyl group to give the 3-arylazetidine (IV) may be effected by several methods including, for example, catalytic hydrogenolysis; treatment with lithium or sodium and ammonia; conversion to the xanthate by treatment with carbon disulphide, methyl iodide and base, followed by tin-mediated reduction; and conversion to the 3-aryl-3-chloroazetidine analogue using an alkylsulfonyl chloride and a base, followed by a reductive dechlorination using sodium, lithium or nickel. Formation of the azetidine (V) is achieved by reaction of (IV) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by either catalytic transfer hydrogenation (e.g. ammonium formate and palladium

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catalyst) or by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (V) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may be prepared directly from the azetidine (IV) without isolation of an intermediate such as the secondary amine (V). For example, when P is a diphenylmethyl group, azetidine (IV) may be treated with phosgene followed by amine R^2NH_2 to give urea (I) directly.

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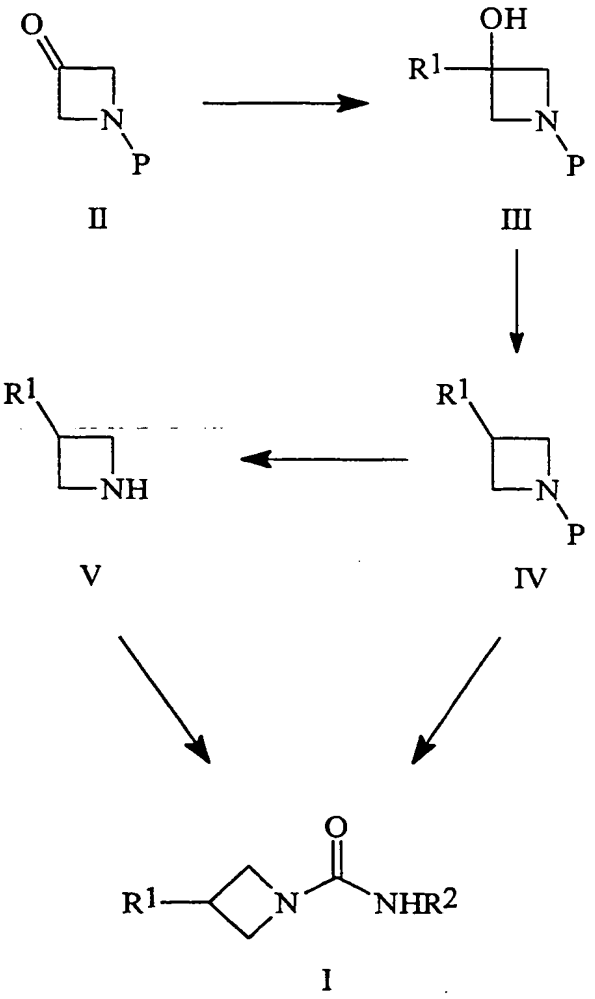
Reaction Scheme



The invention further provides a pharmaceutical composition comprising a compound according to the present invention in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound according to the present invention with a pharmaceutically acceptable carrier or excipient.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for a example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration

by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Antagonism of 3-MPA-Induced Seizures

Several animal seizure models are available for the screening and characterisation of anticonvulsant (antiepileptic) drugs. Most models employ a chemical convulsant to induce seizures and the anticonvulsant potencies of novel compounds are measured in terms of their ability to increase the dose of convulsant required to induce a seizure response (or to prolong the latency to seizure onset following a bolus dose of the convulsant). Most chemical convulsants work by blocking the neurotransmitter function of gamma-aminobutyric acid (GABA), the predominant inhibitory neurotransmitter in the mammalian brain. This can be achieved by blocking the postsynaptic action of GABA using pentylenetetrazol or bicuculline, or via a presynaptic action using a GABA synthesis inhibitor to decrease GABA release into the synapse. In this case, the inhibitor of glutamate decarboxylase (GAD), 3-mercaptopropionic acid (3-MPA), was used as the convulsant challenge agent. Anticonvulsant effects of test compounds were determined by their abilities to significantly increase the dose of 3-MPA required to initiate a seizure response.

Male albino T/O strain mice (obtained from Tuck) weighing 28-40 g were used in these studies. Animals were assigned randomly to treatment groups and vehicle or test drug (at a dose of 30mg/kg) were administered p.o. to groups of 12 animals 60 min before the administration of a bolus dose of 3-MPA intravenously. Immediately following 3-MPA administration, each mouse was placed individually into a cage for observation. The seizure response of each animal was scored quantally as present or absent (response or non-response) during the 5 min period immediately following 3-MPA administration. A seizure response

was defined as the onset of the initial clonic phase of the seizure (abrupt loss of righting reflex accompanied by vocalisation). The seizure threshold (in terms of mg/kg i.v. of 3-MPA required to evoke a seizure response) was determined in each treatment group by a sequential up/down method followed by modified probit analysis of the quantal data. A range of doses of 3-MPA was prepared (12.5 - 200.0 mg/kg i.v.) increasing by a constant geometric factor ($\sqrt[3]{2}$), which was found in pilot studies to generate suitable data for analysis by this method.

In these studies, 3-MPA was obtained from Sigma.

Test compounds were prepared as solutions dissolved in 45% w/v aqueous 2-hydroxypropyl-β-cyclodextrin in distilled water. 3-MPA was dissolved in isotonic saline and its pH adjusted to 6 using 1M sodium hydroxide solution. Drugs were administered in a dose volume of 10 ml/kg body weight. The test results are shown in Table 1.

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Table 1 - Antagonism of 3-MPA-Induced Seizures: Results of Testing

Compound	SC	SV
Example 1	42.7	15.7
Example 2	24.2	18.6
Example 3	21.4	18.6
Example 4	27.3	18.6
Example 5	32.4	15.7
Example 6	59.5	20.6
Example 7	54.4	20
Example 8	100	15.7
Example 9	29.7	14.9
Example 10	95.8	15.6
Example 15	58.4	14.1
Example 19	>200.0[a]	17.2

SC = Seizure threshold after treatment with test drug

SV = Seizure threshold in vehicle-treated group

[a] = No seizures were observed at the top dose of 200mg/Kg i.v. of 3-MPA

Measurement of anxiolytic activity in mice using the elevated zero-maze model.

The elevated "zero-maze" is a modification of the elevated plus-maze model of anxiety which incorporates both traditional and novel ethological measures in the analysis of drug effects (Shepherd, J.K., Grewal, S.S., Fletcher, A., Bill, D.J. and Dourish, C.T.,. Behavioural and pharmacological characterisation of the elevated "zero-maze" as an animal model of anxiety. *Psychopharmacology,* **1994,** *116,* 56-64).

Male Sprague-Dawley rats (Charles River) weighing 300-450 gm are used. Animals are group-housed (5 per cage; cage size: 40 x 40 x 20 cm) in a temperature-controlled environment (20±2°C), under a 12h light-dark cycle (lights on: 08:00 hours). Food and water are made freely available. Four hours prior to testing, animals are transferred to clean cages and moved to the testing room in order to habituate to the testing environment.

The maze is comprised of a black Perspex annular platform (105cm diameter, 10cm width) elevated to 65cm above ground level, divided equally into four quadrants. Two opposite quadrants are enclosed by clear red Perspex walls (27cm high) on both the inner and outer edges of the platform, while the remaining two opposite quadrants are surrounded only by a Perspex "lip" (1cm high) which serves as a tactile guide to animals on these open areas. To facilitate the measurement of locomotor activity, the apparatus is divided into octants by splitting each quadrant into equal halves using high contrast white lines. The apparatus is illuminated by dim red lighting arranged in such a manner as to provide similar lux levels in both the open and closed quadrants (40-60 lux). A video camera, connected to a VCR in an adjacent observation room, is mounted overhead in order to record behaviour on the maze for subsequent analysis.

Chlordiazepoxide hydrochloride [CDP; Sigma Chemical Co. Ltd., Poole], which has previously been shown to display robust anxiolytic-like effects in the zero-maze, serves as positive control. Drugs are typically dissolved in a 45% solution of 2-hydroxy-propyl-ß-cyclodextrin, and administered orally by gavage 1 hour prior to zero-maze testing.

Rats are placed on a closed quadrant and a 5 min test period is recorded on video-tape. The maze is cleaned with a 5% methanol/water solution and dried thoroughly between test sessions. Five behavioural parameters are scored: [1] percentage of time spent on the open areas; [2] frequency of head dips over the edge of the platform when subjects are located in either the open or the end of the closed quadrants; [3] frequency of stretch-attend postures (SAP) from closed to open quadrants, determined when the subject, on a closed quadrant, exhibits an elongated body posture stretched forward with at least the snout passing over the open/close divide; [4] frequency of rearing; and [5] the number of line crossings. Animals are scored as being in the open area when all four paws were in an open quadrant, and in the

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closed area only when all four paws passed over the open/closed divide. All testing is carried out between 1100 and 1700 hours.

An increase in the frequency of head dips is considered to be a measure of anxiolytic activity. The compound of example 6 was found to be effective at a dose of 100 mg/Kg.

CHEMISTRY

1-(Diphenylmethyl)-3-azetidinol (2)

The compound (2) was prepared according to the method of Anderson and Lok (*J. Org. Chem.* **1972**, *37*, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

1-Diphenylmethyl-3-azetidinone (3)

Dimethyl sulfoxide (0.36 mL, 5 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.40 mL, 4.6 mmol) in dichloromethane (20 mL) at -78 °C under an argon atmosphere. The mixture was stirred for 10 minutes then a solution of 1-(diphenylmethyl)-3-azetidinol (1.0 g, 4.2 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was warmed to -50 °C and stirred for 30 minutes. Triethylamine (2.9 mL, 21 mmol) was added and the mixture warmed to room temperature. After 1 hour, water (50 mL) was added and the mixture extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated *in vacuo* to give 1-diphenylmethyl-3-azetidinone (3) as a pale yellow crystalline solid (1.0 g, 99 %) (lit. (S.S. Chatterjee and A. Shoeb, *Synthesis*, 1973,153) m.p. 82°C).

3-(4-Chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4)

To a stirred solution of 4-chlorophenylmagnesium bromide (9.1 mL, 1.0M in diethyl ether) in diethyl ether (80 mL) at -78 °C under an argon atmosphere was added compound 3 (1.8 g, 7.6 mmol) in diethyl ether (50 mL) dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then slowly warmed to room temperature with stirring over 18

hours. The reaction mixture was then partitioned between aqueous ammonium acetate solution (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed (water, brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a pale yellow viscous oil in quantitative yield. A sample purified for analysis by column chromatography on silica gel using 15-30% ethyl acetate-hexane as eluent and subsequent crystallisation from hexane gave 3-(4-chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4), m.p. 108°C. Found: C, 75.42; H, 5.79; N, 3.98. $C_{22}H_{20}ClNO$ requires C, 75.53; H, 5.76; N, 4.00%.

O-(3-(3-(4-Chlorophenyl)-1-diphenylmethyl))azetidinyl)-S-methyldithiocarbonate (5)

To a stirred suspension of sodium hydride (0.4 g of a 60% suspension in mineral oil, 10.4 mmol) (prewashed with hexane) in THF (80 mL) was added dropwise a solution of compound 4 (1.7 g, 4.9 mmol) in THF (80 mL). The mixture was stirred for 3 hours then carbon disulphide (17.6 mL, 0.29 mol) and methyl iodide (6.1 mL, 0.1 mol) were added dropwise. The mixture was stirred at room temperature for 15 hours and then heated to 50 °C while the solvent was removed in a stream of argon. When the volume of the mixture was reduced by half, the mixture was concentrated *in vacuo* to an approximate volume of 20 mL and then partitioned between water and diethyl ether. The organic layer was washed with water and then brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was crystallised from hexane to give *O*-(3-(3-(4-chlorophenyl)-1-diphenylmethyl))azetidinyl)-*S*-methyldithiocarbonate (5) (2.06g, 96%).

3-(4-Chlorophenyl)-1-(diphenylmethyl)azetidine (6)

To a stirred solution of tributyltin hydride (1.8 mL, 6.9 mmol) in dry toluene (40 mL) at reflux under an argon atmosphere was added dropwise, over 1 hour, a solution of compound 5 (2.0 g, 4.6 mmol) in toluene (40 mL). The mixture was heated under reflux for a further 2 hours then was concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica gel using hexane and then 10% ethyl acetate-hexane as eluent. The product was recrystallised twice from hexane to give 3-(4-chlorophenyl)-1-(diphenylmethyl)azetidine (6) (0.4 g, 34%) m.p. 82 °C. Found: C, 78.94; H, 6.06; N, 4.14. $C_{22}H_{20}ClN$ requires C, 79.15; H, 6.04; N, 4.20%.

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3-(4-Chlorophenyl)azetidine (7)

To a solution of compound 6 (0.36 g, 1.1 mmol) in 1,2-dichloroethane (10 mL) containing proton sponge (0.02 g), cooled in an ice-water bath under an argon atmosphere, was added dropwise 1-chloroethyl chloroformate (0.3 mL, 3.1 mmol). The resultant solution was boiled at reflux for 4 hours, cooled and was concentrated *in vacuo*. The residue obtained was mixed with methanol (10 mL) and heated under reflux for 2 hours, then cooled and concentrated *in vacuo* to give the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) which was used without further purification.

Example 1. 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8)

To the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) (approximately 1.1 mmol) in ethanol (10 mL) stirred at 0°C was added sequentially and dropwise allyl isocyanate (0.15 mL, 1.7 mmol) followed by triethylamine (0.3 mL, 2.2 mmol). After 20 minutes the reaction mixture was partitioned between aqueous ammonium chloride and ether. The organic layer was washed (water and then brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude product. The product obtained was purified by column chromatography on silica gel using 20% ethyl acetate-hexane as eluent to give 3-(4-chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8) which was recrystallised from cyclohexane/toluene (0.16 g, 61%), m.p. 112 °C. Found: C, 62.20; H, 6.23; N, 11.40. $C_{13}H_{15}ClN_2O$ requires C, 62.28; H, 6.03; N, 11.17%.

3-(4-tert-Butylphenyl)-1-diphenylmethyl-3-azetidinol (9)

To a stirred solution of 4-tert-butylphenylmagnesium bromide (11.5 mL, 2.0M (Et_2O)) in toluene (50 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (5.0 g) in toluene (100 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 50 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from cyclohexane gave 3-(4-tert-butylphenyl)-1-diphenylmethyl-3-

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azetidinol (9) (6.23 g), m.p. 168-169°C (cyclohexane). Found: C. 83.68; H, 7.97; N, 3.72. $C_{26}H_{29}NO$ requires C, 84.06; H, 7.87; N, 3.77%.

3-(4-tert-Butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10)

To a stirred solution of compound (9) (6.23 g) and N,N-diisopropylethylamine (3.5 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.4 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) m.p. 145°C (hexane). Found: C, 80.30; H, 7.05; N, 3.64. $C_{26}H_{28}ClN$ requires C, 80.08; H, 7.24; N, 3.59%.

3-(4-tert-Butylphenyl)-1-(diphenylmethyl)azetidine (11)

To a stirred suspension of Raney Nickel (8.6 g, wet slurry) in tertiary butanol (50 mL) and toluene (50 mL) was added a solution of 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) in toluene (10 mL). The mixture was heated to 80°C for 6 hours, cooled to room temperature and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 50 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (10% ethyl acetate/hexane) on silica. Recrystallisation from methanol gave 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (3.40 g), m.p. 95°C (methanol). Found: C, 87.84; H, 8.17; N, 3.92. $C_{26}H_{29}N$ requires C, 87.84; H, 8.22; N, 3.94%.

Example 2. 3-(4-tert-Butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (1.0 g) in dichloromethane (10 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (10 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.8 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (30 mL), washed (water, brine), dried (Na_2SO_4),

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concentrated in vacuo and purified by flash column chromatography (50% ethyl acetate-hexane) to give 3-(4-tert-butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12) (0.21 g), m.p. 98-99°C (diisopropyl ether). Found: C, 74.95; H, 8.97; N, 10.25. $C_{17}H_{24}N_2O$ requires C, 74.96; H, 8.88; N, 10.28%.

Example 3. 3-(4-tert-Butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.5 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring propargylamine (0.24 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Trituration with diethyl ether (2 mL) gave 3-(4-tert-butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13) (0.14 g), m.p. 141°C (diethyl ether). Found: C, 75.40; H, 8.19; N, 10.38. $C_{17}H_{22}N_2O$ requires C, 75.52; H, 8.20; N, 10.36%.

Example 4. (R)-3-(4-tert-Butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.50 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.25 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) concentrated in vacuo and purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-tert-butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14) (0.35 g), m.p. 96-97°C (diisopropyl ether). Found: C, 69.59; H, 8.74; N, 9.23. $C_{17}H_{26}N_2O$ requires C, 70.31; H, 9.02; N, 9.64%.

3-(4-Fluorophenyl)-1-diphenylmethyl-3-azetidinol (15)

To a stirred solution of 4-fluorophenylmagnesium bromide (7.0 mL, 1.0M (Et_2O)) in toluene (20 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (1.4 g) in toluene (30 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 20 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (20% ethyl acetate, hexane) gave 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (1.82 g). To a stirred solution of the free base (1.82 g) in ether (5 mL) was added dropwise a solution of oxalic acid (0.49 g) in acetone (1 mL). The mixture was stirred for 5 minutes then filtered to give the oxalate salt hemihydrate (2.23 g), m.p. 75°C (acetone). Found: C, 66.71; H, 5.34; N, 3.04. $C_{24}H_{22}FNO_5.0.5H_2O$ requires C, 66.67; H, 5.32; N, 3.17%.

3-(4-Fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16)

To a stirred solution of 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (4.0 g) and N,N-diisopropylethylamine (3.2 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.25 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine) and dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (2.2 g), m.p. 108-109°C (hexane). Found: C, 75.13; H, 5.46; N, 3.93. $C_{22}H_{19}ClFN$ requires C, 75.10; H, 5.44; N, 3.98%.

3-(4-Fluorophenyl)-1-(diphenylmethyl)azetidine (17)

To a stirred suspension of Raney Nickel (2.0 g, wet slurry) in tertiary butanol (10 mL) and toluene (50 mL) was added a solution of 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (1.9 g) in toluene (20 mL). The mixture was heated to 80°C for 6 hours, cooled and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 30 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), and

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concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (1.5 g), m.p. 65-66°C (diisopropyl ether). Found: C, 83.25; H, 6.35; N, 4.41. $C_{22}H_{20}FN$ requires C, 83.25; H, 6.35; N, 4.41%.

Example 5. 3-(4-Fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18)

To a stirred solution of 3-(4-fluorophenyl)-*N*-(diphenylmethyl)azetidine (17) (0.67 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.5 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18) (0.30g), m.p. 119-120°C (diisopropyl ether). Found: C, 66.61; H, 6.37; N, 11.74. $C_{13}H_{15}FN_2O$ requires C, 66.65; H, 6.45; N, 11.95%.

Example 6. 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.38 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.4 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring propargylamine (0.3 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash column chromatography (50% ethyl acetate hexane) and then crystallised from diisopropyl ether to give 3-(4-fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19) (0.14g), m.p. 141°C

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(diisopropyl ether). Found: C, 67.32; H, 5.65; N, 11.93. $C_{13}H_{13}FN_2O$ requires C, 67.23; H, 5.64; N, 12.06%.

Example 7. (R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.35 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.2 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.2 mL). The mixture was stirred for 18 hrs at room temperature,diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20) (0.21g), m.p. 104-105 °C (toluene/ethanol). Found: C, 61.93; H, 6.97; N, 10.9. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

Example 8. (3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (21)

This compound was prepared from 3-(4-chlorophenyl-1-(diphenylmethyl)azetidine (6) and propargylamine using the procedure outlined in Example 3, m.p. 160 °C (diethyl ether). Found C, 62.85; H, 5.38; N, 10.89 $C_{13}H_{13}ClN_2O$ requires C, 62.78; H, 5.27; N, 11.26%.

Example 9. (R)-3-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (22)

This compound was prepared from compound (6) and (R)-1-amino-2-propanol using the procedure outlined in Example 4, m.p. 92-93 °C (diethyl ether-toluene). Found: C, 58.97; H, 6.38; N, 9.96. $C_{13}H_{17}ClN_2O_2.0.2PhCH_3$, requires C, 60.23; H, 6.48; N, 9.76%.

Example 10: (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (23)

This compound was prepared from compound (17) and (*S*)-1-amino-2-propanol using the procedure described for compound (20). m.p. 102-104°C. Found: C, 61.94; H, 6.72; N, 11.1. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

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3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidin-3-ol (24)

This compound was prepared from compound (3) and 3,4-dichlorophenylmagnesium bromide using the procedure described for compound (4).

3-(3,4-Dichlorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (25)

This compound was prepared from compound (24) using the procedure described for compound (10).

3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidine (26)

This compound was prepared from compound (25) using the procedure described from compound (11).

Example 11. 3-(3,4-Dichlorophenyl)-*N*-(2-propynyl)azetidine carboxamide (27)

This compound was prepared from compound (26) and propargylamine using the procedure described for compound (12). m.p. 105.5-107.5°C.

Example 12. (R)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (28)

This compound was prepared from compound (26) and (*R*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.58; H, 5.33; N, 9.26. $C_{13}H_{16}C1_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

Example 13. (S)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (29)

This compound was prepared from compound (26) and (*S*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.47; H, 5.30; N, 9.18. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

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3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (30)

This compound was prepared from compound (3) and 4-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(4-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (31)

This compound was prepared from compound (30) using the procedure described for compound (10).

3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32)

This compound was prepared from compound (31) using the procedure described for compound (11).

Example 14. (R)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (33)

This compound was prepared from compound (32) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.78; H, 5.75; N, 9.01. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71, N, 9.13%.

Example 15. (S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (34)

This compound was prepared from compound (32) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.75; H, 5.68; N, 9.09. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71; N, 9.13%.

Example 16. 3-(4-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (35)

This product was prepared from compound (32) and propargylamine using the procedure described for compound (12). m.p. 151-155°C.

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3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (36)

This compound was prepared from compound (3) and 3-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(3-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (37)

This compound was prepared from compound (32) using the procedure described for compound (10).

3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (38)

This compound was prepared compound (37) using the procedure described for compound (11).

Example 17. (R)-3-(3-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (39)

This compound was prepared from compound (38) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 81-82°C.

Example 18. (S)-3-(3-(Trifluoromethyl)phenyl)-*N*-(-2-hydroxypropyl)azetidine carboxamide (40)

This compound was prepared from compound (38) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 80-82°C.

Example 19. 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (41)

This product was prepared from compound (38) and propargylamine using the procedure described for compound (12). m.p. 121°C.

Example 20. 3-(4-(Trifluoromethyl)phenyl)-N-azetidine-1-carboxamide (42)

To a solution of 3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32) (8.2 mmol) in dichloromethane (20 mL) at 0°C, was added a solution of phosgene (1.75M in toluene, 10.2 mmol). The reaction mixture was stirred at room temperature for 90 minutes, concentrated *in vacuo*, then redissolved in THF (25 mL), cooled to 0°C and treated with ammonium hydroxide (12.5 mL). The reaction was stirred for 16 h, then water (80 mL) and ethyl acetate (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL), combined organic layers washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated using ethyl acetate (60 mL) to a solid (1.64 g, 81%), mp. 207.5-208.5-°C (ethyl acetate). Found: C, 54.51; H, 4.59; N, 11.41. $C_{14}H_{17}ClN_2O_2$ requires: C, 54.10; H, 4.54; N, 11.47.

Examples 21 to 84 – See Table 2

These producted were prepared using the procedure described for compound 12.

INSDOCID: <WO___9937613A1_I_>

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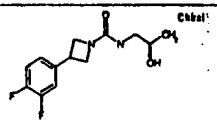
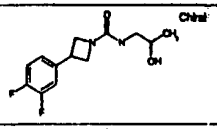
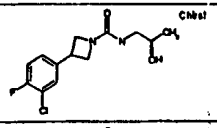
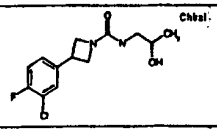
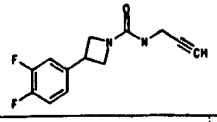
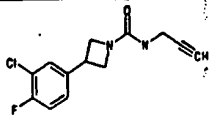
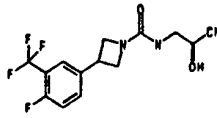
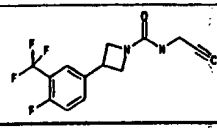
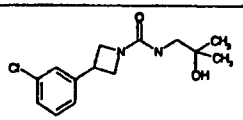
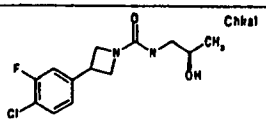
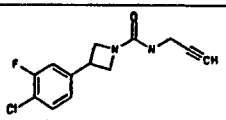
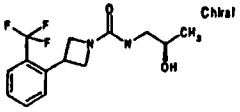
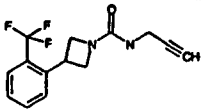
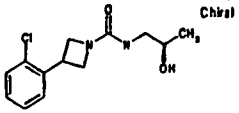
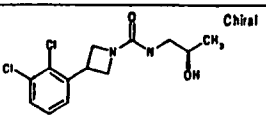
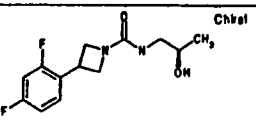
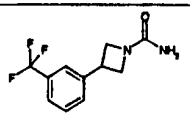
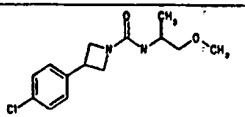
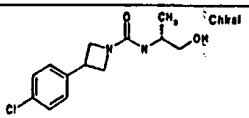
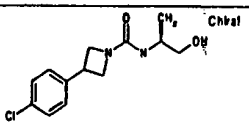
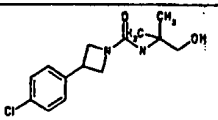
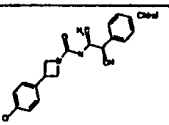
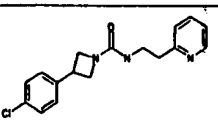
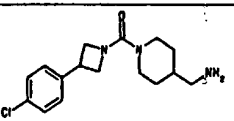
Table 2

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
21	43		C13H16F2N2O2	270.28	108-109	57.79	5.96	10.28	57.77	5.97	10.36	
22	44		C13H16F2N2O2	270.28	108-109	57.73	5.95	10.29	57.77	5.97	10.36	
23	45		C13H16ClFN2O2	286.74	83-84	54.44	5.65	9.74	54.46	5.62	9.77	
24	46		C13H16ClFN2O2	286.74	83-84	54.46	5.69	9.63	54.46	5.62	9.77	
25	47		C13H12F2N2O	250.25	123.0	62.36	4.81	11.20	62.40	4.83	11.19	
26	48		C13H12ClFN2O	266.70	133.0	58.56	4.53	10.45	58.55	4.53	10.50	
27	49		C14H16F4N2O2	320.29	69-71	52.44	5.02	8.69	52.50	5.03	8.74	
28	50		C14H12F4N2O	300.26	119.0	56.05	4.02	9.26	56.00	4.03	9.33	

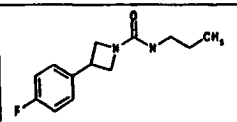
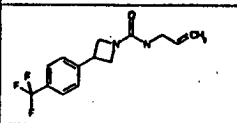
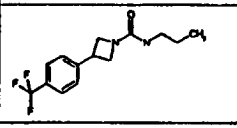
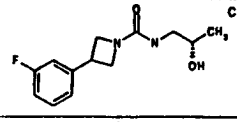
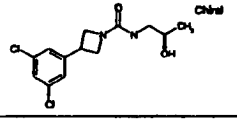
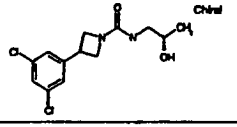
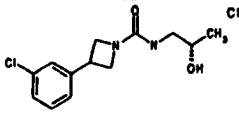
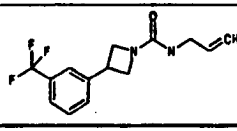
BNSDOCID: <WO___9937613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
29	51		C14H19ClN2O2	282.77	102.0	59.69	6.69	9.80	59.47	6.77	9.90	
30	52		C13H16ClFN2O2	286.74	oil							a
31	53		C13H12ClFN2O	266.70	132.0	58.53	4.58	10.45	58.55	4.53	10.50	
32	54		C14H17F3N2O2	302.30	89.0	55.65	5.64	9.20	55.63	5.67	9.26	
33	55		C14H13F3N2O	282.27	101.0	59.70	4.55	9.96	59.57	4.64	9.92	
34	56		C13H17ClN2O2	268.75	109.0	57.15	6.35	10.28	58.10	6.38	10.42	
35	57		C13H16Cl2N2O2	303.19	111.0	51.43	5.24	9.19	51.50	5.32	9.24	
36	58		C13H16F2N2O2	270.28	88-89	57.74	6.11	10.34	57.77	5.97	10.36	

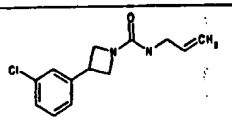
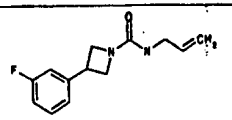
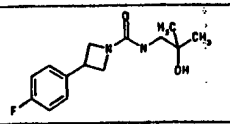
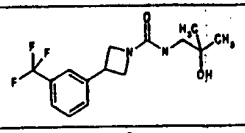
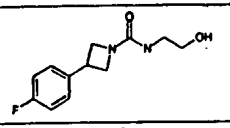
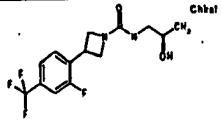
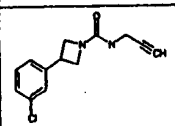
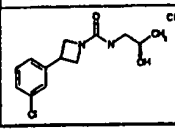
BNSDOCID: <WO___9937613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
37	59		C11H11F3N2O	244.22	198.0	54.14	4.55	11.47	54.10	4.54	11.47	
38	60		C14H19ClN2O2	282.77	110.0	59.33	6.79	9.95	59.47	6.77	9.90	
39	61		C13H17ClN2O2	268.75	71-75							b
40	62		C13H17ClN2O2	268.75	82-85	58.09	6.41	10.36	58.10	6.38	10.42	
41	63		C14H19ClN2O2	282.77	134-135	59.31	6.86	10.02	59.47	6.77	9.90	
42	64		C19H21ClN2O2	344.84	120-122							c
43	65		C17H18ClN3O	315.81	125.0	64.75	5.74	13.27	64.66	5.74	13.30	
44	66		C16H22ClN3O	307.83	137-138	49.82	6.33	10.13	50.55	6.49	10.40	

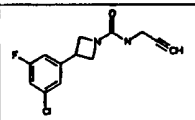
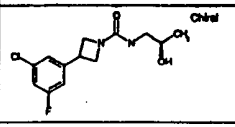
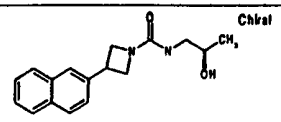
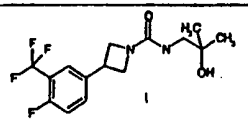
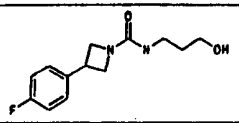
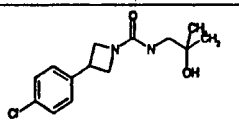
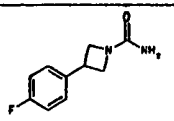
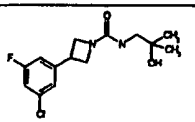
BNSDOCID: <WO__9837613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	N te
45	67		C13H17FN2O	236.29	117-118.5	66.12	7.18	11.83	66.08	7.25	11.86	
46	68		C14H15F3N2O	284.28	136-137.5	59.26	5.39	9.93	59.15	5.32	9.85	
47	69		C14H17F3N2O	286.30	127-128.5	58.69	5.89	10.03	58.73	5.98	9.78	
48	70		C13H17FN2O2	252.29	79.5-80	61.91	6.77	11.09	61.89	6.79	11.10	
49	71		C13H16Cl2N2O2	303.19	110-111	51.67	5.35	9.21	51.50	5.32	9.24	
50	72		C13H16Cl2N2O2	303.19	110-111	52.00	5.41	9.24	51.50	5.32	9.24	
51	73		C13H17ClN2O2	268.75	78-80	58.44	6.13	10.39	58.10	6.38	10.42	
52	74		C14H15F3N2O	284.28	64-66	58.94	5.32	10.15	59.15	5.32	9.85	

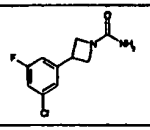
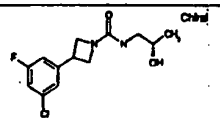
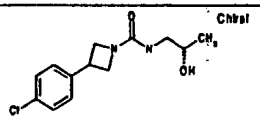
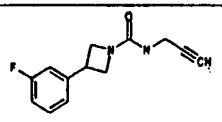
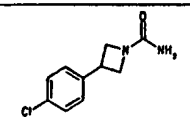
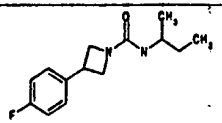
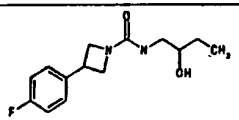
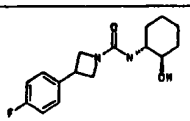
BNSDOCID: <WO___9937613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
53	75		C13H15ClN2O	250.73	65-66	62.75	5.97	11.09	62.28	6.03	11.17	
54	76		C13H15FN2O	234.28	62.5-63.5	66.52	6.52	11.90	66.65	6.45	11.95	
55	77		C14H19FN2O2	266.32	77-78.5	63.25	7.25	10.52	63.14	7.19	10.51	
56	78		C15H19F3N2O2	316.33	94.5-96	57.00	5.85	8.82	56.96	6.05	8.85	
57	79		C12H15FN2O2	238.26	99-101	60.41	6.35	11.72	60.49	6.35	11.75	
58	80		C14H16F4N2O2	320.29	106-107	52.41	5.11	8.71	52.50	5.03	8.74	
59	81		C13H13ClN2O	248.71	90-105 decom.	62.67	5.27	11.10	62.78	5.27	11.26	
60	82		C13H17ClN2O2	268.75	75-76.5	58.18	6.38	10.32	58.10	6.38	10.42	

BNSDOCID: <WO___9937613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	N t
61	83		C13H12ClFN2O	266.70	108.5-110	58.50	4.44	10.53	58.55	4.53	10.50	
62	84		C13H16ClFN2O2	286.74	79-80.5	54.61	5.77	9.69	54.46	5.62	9.77	
63	85		C17H20N2O2	284.36	143-144	71.63	7.11	9.78	71.81	7.09	9.85	
64	86		C15H18F4N2O2	334.32	110-111.5	53.85	5.51	8.34	53.89	5.42	8.38	
65	87		C13H17FN2O2	252.29	90-93	62.09	6.70	10.78	61.89	6.79	11.10	
66	88		C14H19ClN2O2	282.77	114-115.5	59.52	6.88	9.62	59.47	6.77	9.91	
67	89		C10H11FN2O	194.21	205-208.5	61.74	5.70	14.21	61.85	5.71	14.42	
68	90		C14H18ClFN2O2	300.76	112.5-113.5	55.86	6.07	9.33	55.91	6.03	9.31	

BNSDOCID: <WO__9937613A1_I_>

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
69	91		C10H10ClFN2O	228.66	198-200.5							
70	92		C13H16ClFN2O2	286.74	81-82.5							
71	93		C13H17ClN2O2	268.75	92.5-94	58.23	6.41	10.26	58.10	6.38	10.42	
72	94		C13H13FN2O	232.26	101.5-10.25	67.13	5.60	12.03	67.23	5.64	12.06	
73	95		C10H11ClN2O	210.66	oil							d
74	96		C14H19FN2O	250.32	100-102	67.10	7.64	11.05	67.18	7.65	11.19	
75	97		C14H19FN2O2 (0.3 H2O)	266.32	77-79	61.83	7.30	10.39	61.74	7.28	10.29	
76	98		C16H21FN2O2	292.36	141-142.5	65.71	7.31	9.52	65.73	7.24	9.58	

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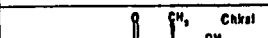
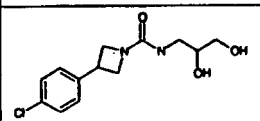
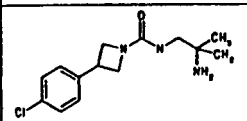
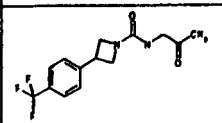
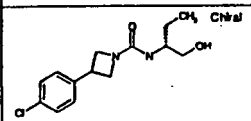
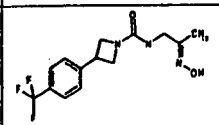
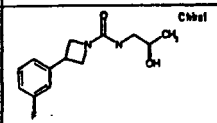
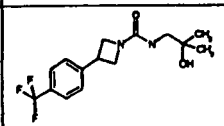
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
77	99		C13H17FN2O2	252.29	118-120	61.59	6.89	10.95	61.89	6.79	11.10	
78	100		C13H17ClN2O3	284.75	90-92	54.93	6.07	9.79	54.84	6.02	9.83	
79	101		C14H20ClN3O.HCl	318.25	183-184	52.76	6.77	13.04	52.84	6.65	13.20	
80	102		C14H15F3N2O2	300.28	139.5-141	56.07	5.05	9.27	56.00	5.03	9.32	f
81	103		C14H19ClN2O2	282.77	oil							e
82	104		C14H16F3N3O2	315.30	>150 decom.	53.05	5.18	13.24	53.33	5.11	13.32	g
83	105		C13H17FN2O2	252.29	77.5-79	61.82	6.83	11.05	61.89	6.79	11.10	
84	106		C15H19F3N2O2	316.33	123-124	57.03	6.08	8.88	56.96	6.05	8.85	

Footnotes for Table 2:

Footnote a: IR: 3373, 3316, 2923, 2855, 1639, 1620, 1557, 1488, 1462, 1434, 1378, 1304, 1153, 815 cm^{-1}.

Footnote b: IR: 3500, 3429, 3346, 3274, 2925, 2854, 1614, 1556, 1466, 1420, 1407, 1052, 824, 536 cm^{-1}.

Footnote c: IR: 3414, 3320, 3253, 2925, 2855, 1606, 1544, 1492, 1460, 1376, 1316, 1092, 822, 751, 705 cm^{-1}.

Footnote d: IR: 3340, 3166, 2923, 2854, 1650, 1613, 1493, 1460, 1378, 1303, 1098, 820 cm^{-1}.

Footnote e: IR: 3310, 2964, 2878, 1632, 1538, 1494, 1482, 1462, 1398, 1328, 1093, 1015, 823, 529 cm^{-1}.

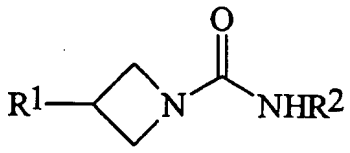
Footnote f: compound (102) was made by the oxidation of compound (33), by methods known to those skilled in the art.

Footnote g: Compound (104) was made from compound (102) by methods known to those skilled in the art.

BNSDOCID: <WO___9937613A1_I_>

CLAIMS

1. A compound of formula (1)



(1)

wherein

R^1 is aryl; and

R^2 is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

2. A compound according to claim 1 wherein R^1 is an aryl group selected from phenyl and naphthyl.

3. A compound acording to claim 1 or 2 wherein R^1 has 1, 2 or 3 substituent groups.

4. A compound according to any preceding claim wherein R^1 is substituted with one or more substituent groups selected from halo, trifluoromethyl and tertiary-butyl.

5. A compound according to claim 4 wherein said halo groups are selected from chloro and fluoro.

6. A compound according to claim 1, 2, 3, 4 or 5 wherein R^1 is a meta- or para-substituted phenyl group.

7. A compound according to claim 1 wherein R^1 is selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

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8. A compound according to claim 1, 2, 3, 4 or 5 wherein R^1 is selected from a 2,3-disubstituted phenyl group, a 2,4-disubstituted phenyl group, a 3,4-disubstituted phenyl group and a 3,5-disubstituted phenyl group.

9. A compound according to claim 8 wherein R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.

10. A compound according to claim 9 wherein R^1 is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.

11. A compound according to claim 1 wherein R^1 is selected from 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

12. A compound according to any one of claims 1 to 11 wherein R^2 is alkyl.

13. A compound according to any one of claims 1 to 12 wherein R^2 is C_{1-8} alkyl.

14. A compound according to any one of claims 1 to 13 wherein R^2 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

15. A compound according to any one of claims 1 to 13 wherein R^2 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

16. A compound according to any one of claims 1 to 13 wherein R^2 is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.

17. A compound according to claim 1 wherein the compound is selected from 3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide, (R)-3-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propenyl)azetidine-1-

carboxamide, 3-(4-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*R*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*S*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide and 3-(4-Trifluoromethyl)phenyl-*N*-azetidine-1-carboxamide.

18. A compound according to any one of claims 1 to 17 for use in therapy.

19. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders.

20. Use according to claim 19 wherein said medicament is for the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.

21. Use according to claim 19 wherein said medicament is for the treatment (including prophylaxis) of anxiety or epilepsy.

22. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 in combination with a pharmaceutically acceptable carrier or excipient.

24. A method of treatment (including prophylaxis) of CNS disorders comprising administering to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 17.

25. A method according to claim 24 wherein said method is for the treatment of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness,

alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.

26. A method according to claim 24 wherein said method is for the treatment of anxiety or epilepsy.

27. A method of muscle relaxation prior to surgery or surgical manipulation or a method of pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to any one of claims 1 to 17.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 99/00223

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D205/04 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 872 447 A (LEPETIT S.P.A.) 12 July 1961 see the whole document	1,2,18, 23
A	EP 0 194 112 A (ROBINS CO INC A H) 10 September 1986 see claims & US 4 956 359 A cited in the application	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 1999	07/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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Form PCT/ISA/210 (second sheet) (July 1992)

NSDOCID: <WO___9937613A1_I_>

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/GB 99/00223

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 24-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

BNSDOCID: <WO 9937613A1 | >

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/00223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 872447 A		NONE	
EP 0194112 A	10-09-1986	AT 52915 T	15-06-1990
		AU 599585 B	26-07-1990
		AU 5388786 A	04-09-1986
		CY 1724 A	06-05-1994
		DK 90086 A	29-08-1986
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		GR 860549 A	24-06-1986
		HK 83893 A	20-08-1993
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		JP 61210031 A	18-09-1986
		PH 25455 A	01-07-1991
		PT 82117 A,B	01-03-1986
		US 4956359 A	11-09-1990
		AU 599312 B	19-07-1990
		AU 5388886 A	04-09-1986
		CA 1294274 A	14-01-1992
		DK 36893 A	29-03-1993
		DK 90186 A	29-08-1986
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		IN 162808 A	09-07-1988
		JP 1965814 C	25-08-1995
		JP 6099386 B	07-12-1994
		JP 61205254 A	11-09-1986
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		US 5068231 A	26-11-1991

BNSDOCID: <WO___9937613A1_I_>